IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOGEN INTERNATIONAL GMBH and BIOGEN MA INC.,	)	
Plaintiffs,	)	Civil Action No. 17-823-MN (Cons.)
v.	)	
AMNEAL PHARMACEUTICALS LLC, et al.	)	
Defendants.	)	

DEFENDANTS' POST-TRIAL FINDINGS OF FACT

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TABLE OF ABBREVIATIONS

Term	Definition
'296 application	U.S. Patent Application No. 12/526,296
'426 application	U.S. Patent Application No. 13/372,426
'514 patent	U.S. Patent No. 8,399,514 (DTX3)
'921 provisional or provisional application	U.S. Provisional Patent Application No. 60/888,921 (DTX2)
AEs	Adverse events
Asserted claims	Claims 1-4, 6, 8-13, and 15-16 of the '514 patent
Biogen	Plaintiffs Biogen International GmbH and Biogen MA, Inc.
CONFIRM trial	Biogen's CONFIRM Phase III clinical trial
CTRB	Clinical Trial Review Board
DEFINE trial	Biogen's DEFINE Phase III clinical trial
DMF	Dimethyl fumarate
dosing section of the specification	Paragraphs at col. 17, l.59 – col. 19, l. 3 of the '514 patent; or Paragraphs 112-117 of the PCT application
EDSS	Expanded Disability Status Score
Gd	Gadolinium
FDA	United States Food and Drug Administration
FP	Forward Pharma A/S
GI	Gastrointestinal
MMF	Monomethyl fumarate
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
Nilsson	International Patent Application Publication No. WO 2006/037342 (DTX324)
PCT application	International Patent Application Publication No. WO 2008/097596 (DTX3)
Phase II trial or Phase II study	Biogen's Phase II clinical trial
POSA	Person of ordinary skill in the art
PTAB	Patent Trial and Appeal Board
PTO	United States Patent and Trademark Office
SAEs	Serious adverse events

I. Background Of U.S. Patent No. 8,399,514

1. U.S. Patent No. 8,399,514, entitled "Treatment for Multiple Sclerosis," issued on Mar. 19, 2013 to named inventors Drs. Matvey Lukashev and Gilmore O'Neill. DTX1_0001. The '514 patent issued from U.S. application 13/372,426, filed on Feb. 13, 2012, which claims priority to U.S. application 12/526,296, filed on Feb. 7, 2008, and U.S. provisional 60/888,921, filed on Feb. 8, 2007. *Id.* Biogen asserted at trial claims 1-4, 6, 8-13, and 15-16. Duddy Tr. 376:6-9.

2. As filed in 2007, the provisional application was entitled "Nrf2 Screening Assays and Related Methods and Compositions." DTX2_0004. Nrf2 is a "transcription factor" that protects cells against oxidative stress and detoxifies substances. Yong Tr. 75:22-76:4; Lukashev Tr. 172:3-18; DTX2_0023-24(¶ 85). Dr. Lukashev, the original sole inventor and "a bench scientist involved in fundamental drug discovery," performed experiments showing that DMF activated Nrf2. Yong Tr. 75:4-8; Lukashev Tr. 172:3-25. Dr. Lukashev filed his application based on the idea that DMF's activation of Nrf2 could be used to "screen for" other compounds that act by the same pathway. *Id*. 182:17-184:14, 186:15-18, 187:2-10. The provisional application is focused on "identifying compounds that activate the Nrf2 pathway so that compounds can be brought forth for potential new protective activities in models of many neurological conditions and to be tested at many different doses." Yong Tr. 80:8-81:14; DTX2_0040-42 (claims 1 and 11).

3. In 2008, Biogen filed its PCT application, under the same title, which was designated in the U.S. as the '296 application. DTX3_0001; *see* DTX1_0001. The specification filed with the PCT application issued as the '514 patent. DTX12_0011-58; Yong Tr. 74:13-15. Dr. O'Neill was not named as an inventor on either application. DTX3-0001; DTX457_0006.

4. The specification is not directed to the discovery of any specific dose of any specific drug to treat any specific disease, let alone the specifically claimed dose of 480 mg/day of DMF to treat MS. Yong Tr. 75:9-21; Lindsey Tr. 141:20-142:3. Rather, the specification is directed to

"screen[ing] through a huge number of compounds for the capacity to activate Nrf2 and to then to take [the newly discovered] promising compounds ... into models of neurological conditions." Yong Tr. 74:25-75:3; *see* DTX3_0001 (Abstract). In Examples 1-3, Dr. Lukashev reported his data showing DMF and MMF activate Nrf2. DTX003_0032-34 (¶¶ 121-29); Lukashev Tr. 178:25-180:15; *see* Yong Tr. 86:2-13. The specification states "the finding that DMF activates the Nrf2 pathway in conjunction with the neuroprotective effects of DMF further offers a rationale for identification of structurally and/or mechanistically related molecules that would be expected to be therapeutically effective for the treatment of neurological disorders, such as, e.g., MS." DTX3_0009 (¶ 32); *see* Yong Tr. 76:9-24; Lindsey Tr. 125:4-19. Based on this "rationale," the specification provides five methods to discover new compounds and new methods for treating neurological diseases: Method 1 for "screening" for new candidate compounds; Method 2 for "evaluating" the neuroprotective properties of such compounds; Method 3 for "comparing" such compounds against known fumaric acid derivatives (i.e. DMF); Method 4 for "treating" a neurological disease with a compound that is "at least partially structurally similar" to DMF or MMF; and Method 5 for "treating" a neurological disease using a compound that upregulates Nrf2 and one that does not. DTX3_0005 (¶ 9); Wynn Tr. 656:6-659:17; Yong Tr. 82:6-25.

5. The specification identifies over 20 billion compounds that are at least partially structurally similar to DMF or MMF that may be "screened, identified, evaluated, or used for treating a neurological disorder" in Methods 1-5. Yong Tr. 84:5-25; DTX3_0016 (¶ 70); *see id.* 0016-19 (¶ 71-78). The specification contemplates that these candidate compounds may treat "a range of neurological conditions" including "[MS] or other demyelinating diseases." DTX3_0026 (¶ 104); Yong Tr. 83:15084:4; Wynn Tr. 608:20-609:6, 664:12-665:2. In total, the specification discusses the potential treatment of 32 neurological diseases. Yong Tr. 83:15-84:4.

6. The specification states that "preliminary doses, for example, as determined in animal tests, and the scaling of dosages for human administration is performed according to art-accepted practices," which a POSA would need to undertake through "animal testing or cell culture testing" (DTX3_0028 (¶ 112) to "transition to treating human disease." Lindsey Tr. 130:20-131:9; *see* DTX3_0028-29 (¶¶ 11214). These potential doses are not directed to MS and "could cover any of the diseases in the patent." Wynn Tr. 669:25-670:5; *see id*. 670:6-671:6, 673:22-674:5; Lindsey Tr. 139:13-17. The specification states that "an effective dose" of DMF—not specific to MS—merely "can be" within a range of "0.1 g to 1 g per [day]." DTX3_0030-31 (¶ 116). As these doses merely ***could be*** effective, for an unspecified disease, a POSA would need to "experiment[] in order to define a particular dose." Yong Tr. 89:22-90:10. As Dr. Lukashev testified, the data in the specification "cannot be used to define clinical dosing." Lukashev Tr. 180:2-15, 189:12-190:8; *see* O'Neill Tr. 578:7-21.

7. From filing the PCT application in 2008 until June 2011, the claims remained directed to the 5 Methods. DTX3_0036-38 (Cls. 1, 8, 9, 14); *see* Lindsey Tr. 149:9-22; Yong Tr. 80:18-81:19. The original claims did not mention dosing of DMF. *Id.* By April 2011, Biogen's Phase III trials showed that 480 mg/day of DMF was effective to treat MS. Dawson Tr. 330:23-3; Lindsey Tr. 148:14-23; DTX406_001. Afterwards, in June 2011, Biogen changed the title from "Nrf2 Screening Assays and Related Methods and Compositions" to "Treatment for Multiple Sclerosis." Lindsey Tr. 149:23-150:1; DTX457_3264. Biogen also "canceled the existing claims [and] replaced them with new claims directed towards treating MS with 480 [mg] a day of either [DMF or MMF]." Lindsey Tr. 148:24-149:22; DTX457_3255-57.

8. In October 2011, Biogen added Dr. O'Neill as an inventor to Dr. Lukashev's application. Lindsey Tr. 150:2-5; DTX457_0120-21. As Dr. Lukashev "did not provide any

clinical input," he understood that Dr. O'Neill was added as an inventor because the "claims were changed to be clinical." Lukashev Tr. 176:2-5; 195:13-21. Dr. O'Neill testified he had not seen the patent before being added to the application. O'Neill Tr. 583:24-584:12.

9. When the examiner repeatedly rejected the new claims as obvious, Biogen argued that "a [POSA] would not have expected the dose of 480 mg/day to be effective in treating MS." DTX457_3115, 3146; *see also* Dawson Tr. 358:10-359:4. The examiner never mentioned written description in those rejections. DTX457_0057-0062, 3231-3235.

10. As issued, all asserted claims 1-4, 6, 8-13, and 15-16 of the '514 patent recite at least these common elements: (1) a method of treating MS, (2) by administering a pharmaceutical composition of DMF, (3) in a therapeutically effective amount of 480 mg/day DMF (or MMF). DTX1_0028-29; Wynn Tr. 596:3-12; Lindsey Tr. 116:19-117:3; Yong Tr. 73:25-74:9.

II. Person Of Ordinary Skill In The Art

11. The POSA to whom the specification is addressed, as filed in 2007 and 2008, would have been "a scientist engaged in laboratory early fundamental research involving potential mechanisms of neurological diseases and drug activity." Yong Tr. 77:18-78:4. This scientist would have had "a Ph.D. in a biological science" and experience with "screening, characterizing, and evaluating neuroprotective properties of drug candidates." *Id.* 78:5-12. Dr. Lukashev, the sole original inventor, has these qualifications: a Ph.D. in "molecular and cell biology" and experience as "a bench scientist involved in fundamental drug discovery." Lukashev Tr. 165:10-166:1, 166:21-167:20, 168:23-169:14; Yong Tr. 75:4-7. The specification's focus on "cellular biochemical molecular assays" and testing "of complicated models of neurological condition[s]," are the tools of laboratory scientists—not physicians. Yong Tr. 71:20-72:3, 94:16-95:9. Dr. Yong is the only expert at trial who applied and meets this definition of a POSA. *Id.* 77:24-78:15.

12. Biogen proposes that a POSA "in 2007 would have at least a medical degree with at least three years of training in neurology and at least three years of clinical experience in treating individuals with multiple sclerosis." Wynn Tr. 595:8-17; Duddy Tr. 374:24-375:9. Drs. Lindsey and Stobbe qualify and applied this POSA definition. Lindsey Tr. 117:9-20; Stobbe Tr. 206:6-23.

III. The Asserted Claims Of The '514 Patent Lack Of Written Description

13. The specification lacks written description for the claimed method of treating MS with a therapeutically effective amount of 480 mg/day DMF. Yong Tr. 71:8-19; Lindsey Tr. 124:2-23. To a research scientist, the specification is directed to "screening and discovery" of "novel compounds that interrupt the Nrf2 pathway," whereas the claims recite "using a specific compound at a specific dose in a very specific disease." Yong Tr. 75:9-21; 79:10-23. Similarly, a neurologist would have understood the specification to describe the discovery of "new pharmaceutical compounds which might be useful for treating a wide variety of diseases," but not "any method of actually treating MS with [DMF] at a specific dose." Lindsey Tr. 141:20-142:3; 139:5-20.

A. The Specification Does Not Support Treating MS With 480 mg/Day Of DMF

1. The Specification Is Directed To The Discovery Of Novel Compounds

14. DMF undisputedly "was known in the art as a treatment of MS." Wynn Tr. 651:15-652:8, 654:2-6. In 1999, Biogen and its predecessor had already filed patent applications directed to treating MS using DMF. *See infra* FOF 51. Indeed, the specification explains that DMF had "been proposed for treatment of MS." DTX3_0008 (¶ 30). The specification focuses on DMF's known activation of the Nrf2 pathway as a "rationale" for identifying similar molecules that activate Nrf2. DTX3_0009 (¶ 32); *see supra* FOF 4. Dr. Lukashev presented this rationale "strictly for discovery" research purposes "at the early stages" to search for "novel compounds." Lukashev Tr. 184:15-185:8, 186:15-18; *see id.* Tr. 173:14-174:14. A POSA would understand that this drug discovery rationale underlies the "five methods listed in the application" directed to "screening

new compounds" and "methods of treatment." Wynn Tr. 655:8-656:13; *see* DTX3_0004-5 (¶ 9). But none of Methods 1-5 teach a method of treating MS by administering a 480 mg/day dose of DMF and/or MMF. *See* Yong Tr. 83:1-14; Lindsey Tr. 125:20-126:23; DTX3_0004-8 (¶¶ 9-24), 0010-15 (¶¶ 40-68). Methods 1-3 are directed only to "discovering compounds," and Method 5 "is not really at issue in this case." Wynn Tr. 608:7-19, 659:6-17.

15. Method 4 recites "treating a neurological disease by administering ... at least one compound that is partially structurally similar to DMF or MMF." DTX3_0004-5 (¶ 9). Method 4 comprises administering "a therapeutically effective amount of at least one neuroprotective compound having Formula I, II, III, or IV, e.g., a fumaric acid derivative (e.g., DMF or MMF)." DTX3_0007 (¶ 19), 0014 (¶ 62-63). Formulas I-IV include "over 20 billion compounds" that are partially structurally similar to DMF and MMF. Yong Tr. 84:5-25; *see* Lukashev Tr. 186:19-187:1. A POSA would understand that Method 4 uses "DMF or MMF as the starting point . . . to look for compounds that activate the Nrf2 pathway." Yong Tr. 83:1-14; *see id.* 100:5-14, 101:22-102:9; *see* Linsey Tr. 126:12-127:6. As Dr. Lukashev testified, Method 4 is "referring to other compounds than DMF or MMF for treating neurological diseases," and was a part of "novel compound discovery efforts." Lukashev Tr. 197:15-198:14; *see id.* 185:22-186:18, 187:2-10.

16. Method 4 is directed to treating "a neurological disease"—not just MS. DTX3_0014-15 (¶¶ 62-64). The specification explains that the "neurological disease[s] in methods 1-5 above can be a neurodegenerative disease such as, for example, ALS, Parkinson's disease, Alzheimer's disease, and Huntington's disease," as well as MS "or other demyelinating diseases." DTX3_0026 (¶ 104); *see* Wynn Tr. 664:12-665:4; Lindsey Tr. 127:7-19. In total, the specification lists over 30 neurological disease targets for Method 4. DTX3_0026-27 (¶¶ 104-107); Wynn Tr. 665:13-666:8; Yong 83:21-84:4. As Dr. Lukashev explained, "[t]hese are diseases

in which Nrf2 was implicated as a potential pathogenically relevant mechanism." Lukashev Tr. 187:15-188:10. The specification states that "in some embodiments of method 4" the treatment "slow[s] or prevent[s] neurodegeneration (more specifically, e.g., demyelination, axonal loss, and/or neuronal death)." DTX3_0014-15 (¶ 64). These characteristics of neurodegeneration are features of many neurological diseases, including a majority of the diseases in the specification. Lindsey Tr. 128:1-129:16; 123:23-124:1; *see* Duddy Tr. 471:13-21.

17. A POSA would also understand that a method directed to slowing or preventing "demyelination, axonal loss, and/or neuronal death" is directed to "laboratory scientists that are developing new drugs," not clinicians. Lindsey Tr. 129:13-130:4. When physicians treat MS, they rely on clinical or radiological assessments of patients—not measures of demyelination, axonal loss, and/or neuronal death, which would require "a biopsy of the brain which is invasive and can cause additional damage." Lindsey Tr. 123:7-22, 118:17-119:18, 120:3-121:3; Duddy Tr. 475:12-477:2. This pathological investigation is conducted in preclinical experiments by laboratory scientists investigating new drugs. *See* Lindsey Tr. 129:23-130:2; Duddy Tr. 476:1-21.

18. Even if Method 4 was directed to MS, it never explicitly teaches administering 480 mg/day DMF to treat MS. Wynn Tr. 659:18-660:15, 661:15-21; DTX3_0004-5 (¶¶ 9-10), 0007 (¶ 19), 0014-15 (¶¶ 62-64), 0026 (¶ 104), 0027-28 (¶¶ 108-10), 0034 (¶ 125-29).

2. The Specification Invites A POSA To Discover Which Potential Doses Of A Compound Might Be Effective To Treat A Neurological Disease

19. The specification's discussion of potential doses shows a lack of possession of the 480 mg/day dose of DMF for treating MS. Lindsey Tr. 137:23-139:4. This dosing section concerns future work that *could* be done to determine a dose suitable for treating one or more of the over 30 referenced diseases using any of the compounds discovered in the Nrf2 assays. *Id.* 131:14-132:1, 134:13-136:5. The specification explains that preliminary, therapeutically effective doses may be

determined in "animal tests" or "cell culture assays." DTX3_0028-29 (¶¶ 112-13); Wynn Tr. 669:17-670:17; *see* Lindsey Tr. 130:20-132:1. These "data obtained from the in vitro assays or animal studies can be used in formulating a range of doses for use in humans" for "all of the diseases that are set forth in the patent." DTX3_0029 (¶ 114); Wynn Tr. 670:21-671:6; *see* Lindsey Tr. 132:2-15. The specification instructs that "[f]or DMF or MMF, an effective amount ***can range*** from 1 mg/kg to 50 mg/kg," or "***can be*** from about 0.1 g to 1g" daily. DTX3_0030-31 (¶ 116) (emphasis added). All of this is hypothetical. It is not a conclusion based on prior studies, but instead a proposed research plan for determining a dose in the future. Lindsey Tr. 131:20-132:1. In this regard, the specification does not say that these amounts of DMF or MMF are, in fact, effective to treat MS, or even that the effective amount "does range" or "will range" within the listed amounts. Wynn Tr. 673:3-12, 669:17-671:6; Lindsey Tr.131:13-135:1;135:21-136:5.

20. The specification does not indicate that the inventors engaged in any of these steps to determine an effective DMF dose. Lindsey Tr. 131:14-132:1. A POSA is left to find which doses are effective for which diseases. *Id*. 133:17-22. The specification has "no data to suggest that [480 mg/day] would be effective for any particular disease*." Id*. 134:23-135:1; *see* Yong Tr. 91:13-22. Identifying various dose ranges that *can be* effective is merely a general disclosure of "a range of doses that [the inventors or a POSA may] want to try in the future." Lindsey Tr. 135:2-9.

3. The Specification Lacks Any Indicia Of Possession Of The Invention

a. No *Ipsis Verbis* Description Of The Claimed Method

21. The specification nowhere describes together all three claim elements of a (1) a method of treating MS, (2) by administering a pharmaceutical composition of DMF, (3) in a therapeutically effective amount of 480 mg/day DMF (or MMF). Wynn Tr. 650:16-651:2, 659:18-660:15, 661:15-21, 669:2-671:4. 672:673:5.

b. No Data Concerning 480 mg/day DMF

22. The specification does *not* provide any clinical data administering DMF to humans, let alone, at 480 mg/day DMF to treat MS. Lindsey Tr. 134:13-135:1; Yong Tr. 91:18-22; Wynn Tr. 694:13-18, 695:13-19. Although the Phase II study was reported in the prior art, the specification never mentions it. Wynn Tr. 675:12-14; Lindsey Tr. 139:5-12; Yong Tr. 91:23-92:8. To a POSA, this would indicate that the "specification as originally written was not about the treatment of [MS] with DMF." Lindsey Tr. 139:13-20; Yong Tr. 92:9-15, 97:9-19.

c. No Working Examples Of A Method Of Treating Humans

23. Examples 1-3 do not show possession of a method of treating MS with 480 mg/day of DMF. Lindsey Tr. 132:19-133:6; Yong Tr. 86:11-87:6. "The examples are not treating humans." Wynn Tr. 695:13-19. Instead, they present data showing that DMF and MMF elevate Nrf2 in cancer cells (Exs. 1 & 2) and the spinal cords of EAE mice (Ex. 3). Yong Tr. 86:4-13. They do not relate to clinical dosing, or show the impact of Nrf2 on any treatment endpoint in humans or animal models. Lukashev Tr. 179:12-17; Yong Tr. 87:3-6, 109:12-20.

24. Dr. Lukashev provided the data and initial drafts of Examples 1-3. Lukashev Tr. 178:21-179:15. As Dr. Lukashev explained, "[t]he nature of the data [in these Examples] is such that it's on a different subject really" than a method of treating MS and has "nothing to do with the efficacy in clinical disease." *Id.* 179:21-180:1. These data are "never directly informing for the purposes of selecting therapeutic dose, not the right models, not the right settings, not the right experiments for that purpose." *Id*. 180:8-15. As such, these Nrf2 data "incorporated into [the] application cannot be used to define clinical dosing." *Id*. 189:12-17; *see id*. 176:6-14. Even with "a strong knowledge of drug mechanism of action," this "would not guarantee a response in MS." Duddy Tr. 477:3-16. Dr. Lukashev testified the claimed dose of 480 mg/day DMF to treat MS would be "impossible to extrapolate directly and immediately from the in vitro data" in the specification. Lukashev Tr. 194:5-9; *see id*. 189:18-190:8.

25. The Examples show that DMF and MMF can activate the Nrf2 pathway, but this is not a relevant endpoint for treating MS. Yong Tr. 86:2-13, 86:22-87:2. In 2007, "there was no understanding that Nrf2 would be important or not in causation or treatment of MS." *Id*. 109:24-110:2; *see id*. 86:17-87:2. Even if a POSA assumed Nrf2 activation had some relevance to MS, the examples "do not provide any guide to dosing and to the treatment of MS." *Id*. 87:3-6. First, if a POSA were to convert the doses administered to mice in Example 3 to human doses using the conversion table provided in Table 2, the doses would amount to 25 mg bid and 75 mg bid in the exemplar 60 kg human, far short of the claimed 480 mg/day dose. Lindsey Tr. 132:2-133:4; Yong Tr. 88:16-89:7. "A POSA would not understand that a 480 [mg] dose has been specified by this example." Yong Tr. 89:8-12. Second, while the EAE mouse model in Example 3 can be a model for studying MS, this is only when relevant "outcome measures" are evaluated. *Id.* 87:7-16, 106:17-107:1. Such measures include clinical signs of disability and preventing "lesions in the brain and spinal cord." *Id*. 88:6-12; *see id.* 109:7-17. Yet, these outcome measures were not evaluated in the specification. *Id*. 88:6-15, 109:18-110:2. Instead, Example 3 merely shows that DMF and MMF "activate Nrf2." *Id*. 86:11-13. A physician "would not look at a preclinical mechanism of action and in any way be certain that you were going to see a clinical effect until you have seen the results of the study." Duddy Tr. 478:13-25; *see id.* 473:7-15, 473:20-474:24.

d. No Supporting Theory Or Rationale

26. Dr. O'Neill testified that he wanted to test DMF doses of 240, 360, 480, and 720 mg/day in Option 1, because "it would be important to understand the impact of the magnitude of the dose and the frequency of dose in driving efficacy." O'Neill Tr. 517:5-24; *see* FOF 42. He hypothesized that "the magnitude of the dose combined with a different frequency would have an impact." *Id*. 537:24-539:8. This theory is nowhere in the specification. The specification mentions therapeutic efficacy only in terms of total daily dose and ignores the impact of the magnitude or

frequency of a given dose. DTX3_0029-31 (¶ 114-16). While a POSA would have known these are important variables to understand, the specification does not teach "which of those factors is important ... for different diseases" nor whether to target "a certain maximum concentration or a certain number of times with a maximum concentration or a certain exposure of the drug over the entire day." Lindsey Tr. 136:25-137:15. The specification only states that "720 mg per day may be administered in separate administrations of 2, 3, 4, or 6 equal doses," with no guide to select the dosing frequency. DTX3_0031 (¶ 116). It does not suggest administering 480 mg/day in 2 divided doses. *Id*. In fact, it is undisputed that administering 360 mg or more in a single dose is intolerable, such that 480 mg once-daily is not viable. O'Neill Tr. 532:22-533:4; PTX042 at 13.

27. The single paragraph in the specification containing the sole mention of 480 mg/day does not provide any reason to select this dose to treat MS, nor is there any "dose response data." DTX3_0031 (¶ 116); Wynn Tr. 677:3-12. Dr. O'Neill testified that he "would not write a sentence" like the one in which 480 mg/day appears. O'Neill Tr. 579:25-580:7.

B. Biogen Relies On A Flawed Written Description Analysis

1. A POSA Could Only Pick Out 480 mg/day DMF From The Specification With Hindsight Knowledge Of The Claimed Invention

28. Dr. Wynn analyzed written description from the view of a POSA with hindsight knowledge of the claims. Wynn Tr. 646:22-647:2, 647:17-648;10. He was first "asked to describe the three elements of the claims" and "picked out the key elements." *Id*. 647:17-648:10, 604:2-9; PDX4-09. He then "went back" and "found" each separate claim element in the specification. *Id.* 648:11-649:15, 629:5-630:3, 631:1-13, PDX4-12-15. In reviewing the specification, he "look[ed] to see if these elements were described ... for the purposes of written description." *Id.* 649:2-15.

29. First, Dr. Wynn "look[ed] for multiple sclerosis and … went back in the spec and … found multiple sclerosis." *Id*. 648:16-22; *see also* 629:6-630:3, 650:5-15, 658:21-25; PDX4-

12-13. But these sections do not teach 480 mg/day DMF as an effective dose to treat MS. Wynn Tr. 650:16-651:2, 659:18-660:15. Then he said he was "going to find DMF" and "went back and found places where it said DMF." *Id*. 648:23-649:1; *see id.* 630:4-13, 660:16-25; PDX4-14. But he admitted that "480 is not mentioned in these paragraphs explicitly" as an effective dose of DMF to treat MS. Wynn Tr. 661:15-21. Finally, he "look[ed] for 480 per day and … went back through the spec to try to look for 480 per day," which he found "[i]n the dosage spec." *Id.* 649:2-7; *see id.* 631:1-13, 666:20-667:2; PDX4-15. He found only a single mention of 480-720 mg among other dose ranges, which he referred to as "the real meat" of the specification. Wynn Tr. 621:23-622:13, 683:18-684:8. But he admitted that the inventors "chose not to" mention MS in this discussion of DMF dose ranges and, thus, a POSA would understand that these potential ranges can be effective for "another neurodegenerative disease that's referenced in the patent." *Id*. 673:3-12, 673:22-674:5. A drug that treats multiple diseases will not necessarily have the same effective dose. Lindsey Tr. 159:2-10; Duddy 447:21-25. Dr. Wynn could not identify any place describing together a 480 mg/day dose of DMF as effective to treat MS. FOF 21.

2. The Specification Lacks Any Blaze Marks To The Claimed Invention

a. The Specification Lists 480-720 mg/day Among Several Dose Ranges That Can Be Effective To Treat An Unspecified Disease

30. The specification states that "an effective dose of DMF or [MMF] ... can be" multiple ranges of oral doses between 100-1,000 mg, as follows:

> For example, an effective dose of DMF or MMR to be administered to a subject orally ***can be*** from about 0.1 g to 1 g per pay, 200 mg to about 800 mg per day (e.g., from about 240 mg to about 720 mg per day; or from about 480 mg to about 720 mg per day; or about 720 mg per day). For example, the 720 mg per day may be administered in separate administrations of 2, 3, 4, or 6 equal doses.

DTX3_0030-31 (¶ 116) (emphasis added). This is the only reference in the specification to DMF at a dose of 480 mg/day and it is "not specific to MS." Lindsey Tr. 134:13-135:1; Wynn Tr.

683:18-684:10; Yong Tr. 90:11-17; *see also supra* FOF 6, 19, 29.

31. To a POSA, the specification is merely stating a range of doses to "try in the future" or "explore" further. Lindsey Tr. 135:2-9; *see* Yong Tr. 89:22-90:10, 90:18-25. In the "drug discovery and development process," this presents a "research plan" that would require animal and human clinical trials to identify a therapeutic dose. Yong Tr. 91:5-22; *see id.* 72:8-73:16. In this exploration, the specification states that an "effective amount may vary with the subject's age, condition, and sex, as well as the severity of the medical condition in the subject," but "[t]he appropriate therapeutically effective doses can be selected by a treating clinician." DTX3_0030 (¶ 115). A POSA would understand that experimentation would be required "to figure out the appropriate dose" because the specification "does not" "teach [] how to determine an appropriate dose" based on these listed factors. Lindsey Tr. 133:7-134:12.

32. The dosing section of the specification provides "no data to suggest that [480 mg/day of DMF] would be effective for any particular disease." *Id*. 134:23-135:1. As Dr. Wynn concedes, the rationale for "the reason why [to select 480 mg/day DMF] is not listed" in the dosing section of the specification. Wynn Tr. 677:3-6.

b. DMF Doses In The Identified Ranges Were Ineffective To Treat MS

33. A POSA would have known from the Phase II study that DMF was "ineffective at 360 [mg/day doses] and below" to treat MS. Wynn Tr. 681:7-682:6; *see* Lindsey Tr. 137:23-138:15; DTX441_0001; DDX-1115. The specification states that "an effective dose of DMF…can be" within the ranges 100-1,000 mg/day, 200-800 mg/day, or 240-720 mg/day. DTX3_0030-31 (¶ 116). A POSA reading the specification would have known that the lower portions of these ranges "included doses that [do not] work against [MS]." Wynn Tr. 684:11-14; *see id*. 675:15-676:12. Since the inventors included doses known to be ineffective to treat MS, among doses that can be "effective," a POSA "would conclude that they are also considering treating other diseases

where the effective dose [of DMF] might be different." Lindsey Tr. 138:6-139:4.

34. The inclusion of known ineffective doses for MS further undermines Dr. Wynn's arguments about "nesting" the 480 mg/day dose and "linking" to the 720 mg/day known dose. *See* DTX3_0030-31 (¶ 116); Wynn Tr. 624:9-23. The paragraph "calls out 720 individually"—not 480 mg/day. Wynn Tr. 679:13-680:7. The paragraph further describes dose ranges starting at both 240 and 480 mg/day and ending at 720 mg/day. *Id*. 678:4-13, 681:7-682:6; DDX-1114. A POSA would not conclude that the lower doses in these ranges are effective to treat MS merely by "linking" to 720 mg/day, because doses of 360 mg/day and less, including 240 mg/day, were known to be ineffective. *See* Yong Tr. 91:1-4. Since the lowest doses in the other listed ranges are ineffective for MS (e.g., 100 mg, 200 mg, and 240 mg/day), and no other guidance is provided, there is nothing to lead a POSA to understand the 480 mg/day is effective for MS, let alone preferred, simply because it is disclosed in a range with 720 mg/day. *See id*.

c. The Specification Relies On A Mere Hope That 480 mg/day DMF Can Be Effective, Yet Biogen Argues That Would Be Unexpected To A POSA

35. Dr. Wynn testified that, if he had seen the application in 2007, he "wouldn't know if [480 mg/day] was clinically effective" and that, based on the Phase II study, a POSA would be "surprised that 480 [mg/day] was efficacious." Wynn Tr. 694:13-18, 688:6-13; *see id.* 688:14-17, 688:24-689:9, 689:20-690:18. The prior art "would effectively teach away from the invention," since a POSA "would go to 720 [mg/day] or higher [as] that was the lowest effective dose in the Phase II study." *Id*. 703:24-704:5. Even "upon reading the '514 application," Dr. Wynn would have been "terribly surprised" that 480 mg/day DMF would exhibit "clinical efficacy or statistically have an effect . . . in a Phase III trial." *Id*. 693:6-23; *see id.* 690:19-691:2.

36. Consistent with this, Biogen also argued to the PTO that "a [POSA] would not have expected the dose of 480 mg/day to be effective in treating MS." DTX457_3115; *see*

DTX457_3117. Biogen submitted the declaration of Dr. Dawson, who opined that a POSA "would not have a reasonable expectation that the 480 mg/day dose would provide ... clinically meaningful effectiveness for treating MS." DTX457_3146; Dawson Tr. 358:10-359:4.

37. Although Dr. Duddy attempted to add "nuance" at trial, he argued in his expert report that "a [POSA] would not have expected that administering 240 milligrams b.i.d. [DMF] would be effective in treating MS." Duddy Tr. 490:13-491:16. He further argued that "one skilled in the art would not have expected that administering 480 milligrams a day [DMF] would be effective in treating MS." *Id*. 491:24-492:6. He testified that, based on the Phase II study, "it would be pure speculation what happens between 360 and 720." *Id*. 492:7-493:4; *see id.* 489:14-490:12. "To have a reasonable expectation of using a dose less than 720" mg/day, in addition to the Phase II study, he would need "at least one more data point[] on either side of 720 that was going to allow [him] to get a meaningful dose response curve." *Id*. 481:10-483:8.

38. The specification provides "no new information" regarding "using DMF to treat MS at a particular dose." Lindsey Tr. 139:13-20. Indeed, none of the Phase II or Phase III data, nor any clinical data, is provided in the specification. Duddy Tr. 493:11-25. As Dr. Wynn conceded, "there's no data on [the 480 mg/day DMF dose] provided in the specification." Wynn Tr. 694:13-18. As such, in reading the patent, Dr. Wynn was left to presume that "the inventor knows [information he's] not privy to and is not included in the specification." *Id*. 691:3-18.

C. Biogen's Arguments In A Related Interference Demonstrate The Lack Of Written Description Of The '514 Patent

39. The PTAB initiated an interference proceeding between Forward Pharma's ("FP") '871 application (published as Nilsson), and Biogen's application, relating to the same claims that issued in the '514 patent. *See* DTX377_0016, 0031. There Biogen argued that FP's application lacked written description" because the "specific combination of disease, effective daily dose, and

drug is nowhere in [FP's] specification." DTX377_0016. Biogen argued:

> [The specification] indiscriminately lists doses ranging from 240 mg to 1080 mg . . . and it states that the daily dosage depends on a number of factors including the 'condition or disease to be treated.' . . . Moreover, [it] provides no guidance to select a 480 mg/day dose over any of the other amounts for any disease, much less for MS specifically."

DTX377_0026 (referring to DTX324_0037-38); *see* Lindsey 140:17-141:2. Both the PTAB and the Federal Circuit found FP's specification lacked written description support. *Biogen MA Inc. v. Forward Pharma A/S*, Interference No. 106,023 (P.T.A.B. Mar. 31, 2017); *FWP IP ApS v. Biogen MA Inc*., 749 Fed. Appx. 969, 973 (Fed. Cir. 2018).

D. After Obtaining The Phase III Results, Biogen Filed An Application Directed To The Claimed Method Of Treating MS With 480 mg/day DMF

40. Shortly after Biogen obtained its Phase III results, Biogen employees Drs. Dawson and O'Neill filed U.S. patent application 2014/0163100, claiming a method of treating MS by orally administering 480 mg/day of DMF. DTX166_0030 (cls. 1 & 2); Dawson Tr. 359:24-360:5; 361:25-362:3. Their application expressly encompasses "methods and compositions for treating [1] a subject having multiple sclerosis … [2] and is administered about 480 mg per day [3] of a fumarate (e.g., [DMF], [MMF], or a combination thereof)." DTX166_0020 (¶ 2). The examples provide data from clinical trial testing of 480 mg/day DMF. Dawson Tr. 361:17-362:24.

IV. The Asserted Claims of the '514 Patent Are Invalid for Lack of Enablement

41. The '514 patent specification fails to enable the claimed method of treating MS. The specification instructs a POSA to do "an enormous amount of work and testing" to show 480 mg/day DMF is therapeutically effective to treat MS. Lindsey Tr. 142:14-19. That is, the dosing section instructs a POSA to "start with preclinical studies including cell culture and animal" models, while "look[ing] at toxicity and efficacy," and then "translate the animal dose into people." Lindsey Tr. 142:20-143:3; *see* Yong Tr. 92:16-93:12. The fact that the number "480" is written in the specification once provides no information or guidance to a POSA to "pick[] that particular

number of the other numbers that are" in the disclosed ranges. Lindsey Tr. 143:11-17.

V. The Asserted Claims Are Invalid for Derivation and Improper Inventorship

A. Dr. O'Neill Presented A Dosing Research Plan Including 480 mg/day That Was Rejected By Biogen

42. On February 19, 2004, Dr. O'Neill presented several dosing options to the CTRB governing Biogen's Phase II study design. O'Neill Tr. 546:5-14; 549:5-8; Bozic Tr. 828:15-19; PTX042 at BiogenF0012333. The proposed doses included 120 mg/day, 120 mg/day BID (240 mg/day), 120 mg/day TID (360 mg/day), 240 mg/day BID. (480 mg/day), 360 mg/day TID (720 mg/day), and 360 mg/day TID. (1080 mg/day). PTX042 at BiogenF0012333; O'Neill Tr. 549:9-12. Dr. O'Neill testified that he did not know which doses would be effective and thought all "could" be effective. *Id*. 560:8-10; 562:2-15; 559:16-22; 543:12-14. There is no contemporaneous evidence showing that he believed 480 mg/day specifically would work. *Id.* 571:20-25; Dawson Tr. 354:23-355:17. In fact, Dr. O'Neill did not even know whether DMF alone would work in treating MS. O'Neill Tr. 556:19-24. As he testified, "[t]he plan was to execute the phase II study to determine ***if indeed DMF would actually have an impact on MRI brain activity*** and then we would go from there." *Id*. 558:25-559:6; *see* Dawson Tr. 357:11-15 ("We hadn't tested [480 mg/day] at that time, so neither one of us knew exactly" [whether it would work].); Bozic Tr. 847:1-3, 851:13-24. Thus, Dr. O'Neill had a research plan to test a series of doses of DMF to investigate their effectiveness in treating MS. He preferred Option 1, testing 240, 360, 480, and 720 mg/day DMF, because it was the "most scientifically rigorous design" and allowed for "dose exploration in addition to dose frequency exploration." PTX386 at BiogenF10113121; O'Neill Tr. 515:12-516:10. But Biogen rejected Option 1 and the 480 mg/day dose, and instead chose to test only 120 mg/day, 360 mg/day and 720 mg/day. DTX94; O'Neill Tr. 558:13-24, 562:20-23.

43. Following the Phase II study and before a decision was made to test 480 mg/day,

Dr. O'Neill chose to leave Biogen's DMF program, leaving the Phase III dosing decision to others. O'Neill Tr. 541:22-542:6, 573:5-574:1, 584:13-19. In addition to leaving the program, Dr. O'Neill does not appear to have been involved in prosecution of the '514 patent. He could not recall even seeing the provisional or PCT applications prior to 2011, when he was added as an inventor. O'Neill Tr. 583:24-584:2. He further admitted that he "did not carry out th[e] experiments disclosed in Examples 1-3 (O'Neill Tr. 577:14-16), he "did not generate th[e] data" providing in the specification's dosing section (*id*. 578:22-579:10), and he did not insert the sole reference to 480 mg/day into the specification. *Id*. 579:25-580:7 ("I would not write a sentence like that.").

B. Biogen Actively Avoided Testing 480 mg/day For Commercial Reasons

44. Biogen was commercially motivated to develop the 720 mg/day dose, as the only dose that would "ensure sufficient revenue for commercial viability." DTX303_0008; *see* DTX038_0002 ("higher dose, higher price"). The clinical team "underst[ood] the commercial constraint (720 mg is the only viable dose)." DTX039_0001. Thus, Biogen actively avoided testing the potentially safer and more convenient 480 mg/day bid dose, out of fear of "the danger of a sub-720 dose in MS pulling down the price to an acceptable level." DTX101_0001; *see* DTX302_0001 ("With MS, patients will be more willing to stay on a TID because they can't 'see' their disease. Although TID is not very convenient."); O'Neill Tr. 550:19-23, 552:3-12; Sibold Tr. 263:1-16.

C. Biogen Never Would Have Tested 480 mg/day DMF But For the FDA

45. When discussing its dose selection for Phase III trials with the FDA, Biogen only proposed 720 mg/day. Dawson Tr. 346:11-347:10; Bozic Tr. 851:1-3; *see also* DTX102_0103 ("[T]he 240 mg TID [DMF] is the dosage with the most favorable benefit/risk profile, and subjects in the Phase 3 studies . . . will receive 240 mg TID."). However, when preparing for its meeting with the FDA to discuss its Phase III trial designs, Biogen personnel were concerned the FDA might disagree with its proposal to test only 720 mg/day:

> As you are aware, as a question regarding the relevance of the dose selection will be asked by the FDA, can we try to include arguments for not having developed 240 mg bid… which is the weakness of the dose selection process (this question may be asked by the FDA….)

DTX063_002. Thus, Biogen considered the 480 mg/day dose only as a "contingency plan" in the event it received pushback from the FDA. PTX110 at BiogenF10157651 ("Team needs to develop contingency plan to prepare for potential FDA concerns with our dose selection rationale"); PTX112 at BiogenF10157649 ("FDA may not be satisfied that we have demonstrated a minimally efficacious dose of [DMF]"); Dawson Tr. 348:11-350:10, 351:5-8.

46. Biogen's claim to only need agreement with the FDA on the maximum dose is belied by the fact the FDA thought it was important to recommend testing a lower dose. Dawson Tr. 352:20-353:3. The FDA advised Biogen to "***consider testing intermediate doses in the Phase 3 study e.g., 240 mg b.i.d. or 120 t.i.d.***," identifying the 480 mg/day dose. DTX463_0004-5 (emphasis added); Stobbe Tr. 230:14-231:4. Biogen initially resisted in its meeting with the FDA, stating 720 mg is "the best choice" for Phase III. DTX463_0005; Dawson Tr. 354:2-15.

47. On September 7, 2006, after the FDA meeting, Biogen, including Dr. Lukashev, discussed that a "240 mg BID arm will be added" to the Phase III trials "based on feedback from FDA." DTX071_001; Lindsey Tr. 147:5-22. "Following FDA's advice . . . Biogen Idec revised the Phase 3 study design to include . . . the 240 mg BID (480 mg/day) dose." DTX080_0002.

VI. The Asserted Claims Of The '514 Patent Are Obvious

48. The claimed method of treating MS with a therapeutically effective amount of 480 mg/day DMF would have been obvious to a POSA. Stobbe Tr. 205:9-206:1, 244:12-25.

A. The Claimed Method Of Treatment Is Directed To A Highly Skilled POSA

49. Both parties assessed obviousness from the perspective of a POSA as defined by Biogen, who as of February 8, 2007, has an M.D., at least 3 years of training in neurology, and at

least 3 years of clinical experience treating MS. Stobbe Tr. 206:6-18; Duddy Tr. 374:24-375:9.

B. The Scope and Content of the Prior Art Teach All Claim Limitations

50. DMF was known to be therapeutically effective to treat MS. Duddy Tr. 392:24-393:22; Wynn Tr. 651:15-652:8; Stobbe Tr. 207:17-208:7, 215:14-216:3, 222:24-223:8.

1. Joshi References Teach Treating MS with DMF

51. The Joshi references are a family of patent publications that claim priority to a 1999 application filed by Fumapharm, which was acquired by Biogen. DTX340 (filed Oct. 29, 1999 and issued Jan. 21, 2003); DTX338 (filed Jul. 17, 2002 and published Jan. 23, 2003); DTX341 (filed Jul. 17, 2002); DTX182 (priority to Oct. 29, 1999); Stobbe Tr. 207:2-12; Hofmann Tr. 791:8-20, 792:7-793:10. The last patent expires Jun. 20, 2020. DTX483_0001-2. The Joshi references teach a "method of treating [MS] ... with an amount of a pharmaceutical preparation [containing DMF and/or MMF] effective for treating [MS]." DTX341_0007 (claim 1); *see* Stobbe Tr. 207:13-208:7; DTX341_0004 (1:26-32), 0005 (4:26-27); DTX182_0007, 0008, 0010; DTX338_0002, 0003; DTX340_0002, 0003.[1] A POSA would have known, by Jan. 5, 2005, that the Joshi applicants were seeking a method of treating MS with DMF. Stobbe Tr. 208:8-209:15; DTX321_0498, 0515 (claim 124), 0517 (claim 143); Hofmann Tr. 796:4-24. As Dr. Duddy testified, the Joshi references provide a "clear steer" to focus on treating MS with DMF. Duddy Tr. 457:19-458:9. Thus, a POSA would have sought to find the effective dose range of DMF. Stobbe Tr. 209:16-23.

2. The Phase II Study Confirmed The Effectiveness Of DMF To Treat MS

52. In 2005 and 2006, Biogen publicly announced a Phase II study of DMF for the treatment of MS. DTX328 (Jun. 2005); DTX320 (Sep. 2005); DTX319 (Jan. 2006); DTX329

[1] The '999 and '001 patents specifically claim treating MS with DMF. DTX341_0007; DTX182_0010. Biogen has never disclaimed these as not enabled. In fact, Biogen has asserted both patents in this action, as well as the '001 patent against Banner Life Sciences, to keep them off the market. *Biogen Int'l GmbH v. Banner Life Sciences LLC*, C.A. No. 18-2054-LPS (D. Del.).

(May 2006); DX327 (May 2006); DTX441 (May 2006); *see* DDX-311.

53. The Phase II Study was a 48-week "dose-ranging study" to determine the efficacy and safety an oral formulation of DMF to treat MS. Stobbe Tr. 211:11-17; DTX320_0001-3; DTX329_0001, 0009. In the study, 257 MS patients were randomized into 4 treatment arms: (i) placebo, (ii) 120 mg/day DMF (120 mg QD), (iii) 360 mg/day DMF (120 mg TID), and (iv) 720 mg/day DMF (240 mg TID). Stobbe Tr. 211:21-212:8. DMF was administered as 120 mg oral capsules. *Id.* 219:17-24, 229:20-230:13. Only patients assigned to 720 mg/day were administered a lower dose initially to build tolerance to DMF. *Id.* 212:9-20, 213:10-13; DTX320_0003. Prior studies reported tolerance issues, especially at higher DMF doses, with common side effects of flushing and GI disturbances. Stobbe Tr. 212:9-213:9.

54. The Phase II primary outcome measure was the total number of Gd-enhancing lesions over four MRI scans. Stobbe Tr. 213:14-214:6; Duddy Tr. 391:9-392:8; DTX320_0004; DTX329_0007. Phase II studies in MS "quite commonly" use MRI scans as the primary endpoint, because they are "more sensitive" than clinical outcomes and can be completed "in a shorter period of time and with a fewer number of subjects" than a Phase III study. Stobbe Tr. 213:14-214:6; *see* Duddy Tr. 384:8-385:12.

55. In January 2006, Biogen announced that the Phase II study "met its primary endpoint," with "a statistically significant reduction in the total number of gadolinium-enhancing brain lesions as measured by MRI with six months of treatment versus placebo." DTX319_0001. In view of the published study protocol (DTX320_0003), a POSA would have learned that one or more of 120, 360, or 720 mg/day DMF was effective to treat MS. Stobbe Tr. 215:19-216:13.

56. In May 2006, Biogen publicly presented additional results from the Phase II study. DTX327; DTX329; DTX441. Each publication confirmed that 720 mg/day DMF was effective to

treat MS by significantly reducing MRI brain lesions by 69% against placebo. Stobbe Tr. 222:24-223:8, 223:14-20, 227:4-11; Duddy Tr. 391:9-392:8, 484:8-22; Wynn Tr. 602:2-19, 685:21-686:1; DTX329_0012-15, 0020; DTX327_0003; DTX441_0001. While the Phase II study also suggested a trend in efficacy for 120 and 360 mg/day DMF, these doses were not statistically significant in reducing brain lesions. Stobbe Tr. 223:9-13; DTX329_0012. Biogen reported that DMF "significantly reduces brain lesion activity, in a dose-dependent manner, as measured by MRI in patients with RRMS over 24 weeks of treatment." DTX327_0003.

57. The Phase II serious adverse events (SAEs), which correlate to safety, showed that the three doses tested were generally safe, with "comparable" SAEs to placebo. Stobbe Tr. 224:16-225:12; DTX329_0017. DMF at the highest dose of 720 mg/day was shown to be safe. Duddy Tr. 429:4-10.

58. DMF, however, showed a dose-related tolerability effect. Stobbe Tr. 225:13-226:9. As with prior experience, the Phase II adverse events (AEs) showed "elevation of some of the side effects that were expected," especially GI side effects at the highest dose of 720 mg/day, which can impact tolerability and limit long-term treatment, even though it is safe to administer. *Id.*; DTX329_0018; DTX441_0002. Dr. Duddy dismisses these tolerability issues to emphasize that DMF was not unsafe. He does not challenge the increased incidence of AEs, but only asserts that they were not so severe to "discontinu[e]" or otherwise rise to a "serious adverse event[]." Duddy Tr. 426:15-427:9. A POSA would still understand these tolerability issues to be undesirable. Stobbe Tr. 225:13-25. Further, despite the up-titration of the 720 mg/day arm to build tolerability to DMF, the AEs were still higher than those at a lower doses of DMF. Stobbe Tr. 212:9-213:13, 226:10-17; DTX329_0018.

59. The May 2006 Phase II publications were co-authored by several people who

contributed to the study design and review. DTX329_0001; DTX327_0003; DTX441_0001. For instance, Dr. Kappos presented the results in May 2006 and was listed as the first author. *Id.* A contemporaneous report of the co-authors' contributions to the Phase II study reflect that Dr. Kappos, "as chair of [the Phase II] study's steering committee . . . was involved in drafting and amending the study protocol and statistical analysis plan, overseeing the conduct of the study, and reviewing statistical analysis." DTX451_0001, 0009; O'Neill Tr. 569:12-570:6. Dr. Minhua Yang "participated in study design and data analysis [and] served as study statistician." DTX451_0009; O'Neill Tr. 568:3-13, 568:24-569:1, 570:7-571:5. Dr. O'Neill "participated in study design, patient recruitment, data collection and analysis, [and] safety review." DTX451_0009. But he did not have sole control over the Phase II study, as shown by the CTRB's rejection of Option 1. Lansden Tr. 272:5-11, 275:12-17; Sibold Tr. 261:24-262:16.

60. Biogen argued during prosecution of the '514 patent that "[t]he results of the Phase 2 clinical study [] were available as of June 2006" and a POSA "at the time of the invention would have been aware of the Phase 2 clinical study ... that involved the use of [DMF]." DTX12_0446-47; *see* Stobbe Tr. 221:2-14. It relied on a POSA's knowledge of the Phase II results to argue that the claimed invention showed unexpected results. DTX12_0453-56, 0844-49, 0907.

3. Nilsson Teaches Administering 480 mg/day DMF To Treat MS

61. Nilsson published on Apr. 13, 2006 and claims priority to Jun. 16, 2005. DTX324_0001. It teaches pharmaceutical compositions of fumaric acid esters, particularly DMF. Stobbe Tr. 233:7-14; DTX324_0003 (1:4-5), 0009-10 (7:30-37, 8:13-16), 0060 (claim 27). The active substances, including DMF, are administered in daily doses ranging from 240-1080 mg, including 480 mg/day in 1, 2, or 3 divided doses of a capsule or tablet. Stobbe Tr. 233:15-22; DTX324_0038-39 (36:13-37:2). For instance, it teaches administering DMF in 120 mg increments, including for a total of 480 mg/day DMF. DTX324_0037-38 (35:26-36:5). These

pharmaceutical compositions are suitable to treat a variety of diseases, including MS. Stobbe Tr. 233:23-234:4; DTX324_0039-40 (37:17-38:9), 0041 (39:11-20), 0062 (claims 44-45). They may be administered for more than 12 weeks. Stobbe Tr. 234:5-10; DTX324_0009 (7:20-21).

C. A POSA Would Have Been Motivated To Administer 480 mg/day DMF (240 mg BID) And Reasonably Expect That It Would Be Effective To Treat MS

1. There Was A Motivation To Determine The Lowest Effective Dose

62. A POSA would have sought to find the "lowest effective dose of DMF" to treat MS to best balance safety and tolerability. Stobbe Tr. 205:17-206:1, 215:19-216:13, 219:4-24, 227:12-25, 244:12-25. This objective of dose selection is widely accepted, as reported in the "well-known" 1994 ICH guidelines. Duddy Tr. 454:6-16; Stobbe Tr. 216:14-217:8. They report that:

> Knowledge of the relationships among dose, drug-concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. This information can help identify ... a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects.... Historically, drugs have often been initially marketed at what were later recognized as excessive doses … This situation has been improved by attempts to find the smallest dose with a discernable useful effect or a maximum dose beyond which no further beneficial effects is seen . . . .

DTX323_0005. A POSA would understand that determining the lowest effective dose increases "the likelihood ... [of] controlling or reducing side effects" improving "tolerability and adherence." Stobbe Tr. 217:9-218:3, 228:23-229:19, 243:11-19; *see* DDX-325. The literature "encourag[es] people to do well designed trials to make sure drugs were not inadequately investigated or launched [] at the wrong dose." Duddy Tr. 454:6-16. Dr. Duddy admits this is "common sense." *Id.* As the Phase II study showed increased AEs at 720 mg/day, the motivation to find the lowest effective dose would have been particularly strong. *See* FOF 58.

63. The lowest effective dose can also reduce the frequency of administration, which is "important, especially if you're treating a chronic condition like [MS]." Stobbe Tr. 218:4-12. Several studies have shown that "that once or twice daily regimens are associated with better

[patient] adherence" than thrice daily dosing. *Id.* 218:13-219:3; DTX334_0016. The prior art taught administering DMF twice daily, including 480 mg/day divided into two equal doses. Stobbe Tr. 231:14-232:7, 233:15-22; DTX332_0002; DTX324_0037-38.

64. A POSA would have known that the risk of excessive DMF doses is an increased likelihood of "dose-related side effects," e.g., flushing and GI issues, which can be problematic for a chronic treatment. Stobbe Tr. 250:2-22. Higher doses would also require either more frequent administration or more drug with each administration. *Id.* 250:23-251:10. Both raise concerns of tolerability and adherence. *Id.*; *see* Lindsey 137:16-22; PTX042, BiogenF70012332.

65. Dr. Duddy opined that, after the Phase II trial, a POSA would "know nothing" about the "blank zone" between 360 and 720 mg/day. Duddy Tr. 482:17-483:8. He alleged "complete ignorance" of any efficacy before and after the "one data point" at 720 mg/day. *Id*. He believed that 720 mg/day provided only "minimum efficacy" in the Phase II study, so this would have "steer[ed]" a POSA to try only higher, not lower, doses. *Id.* 483:24-484:1, 484:23-485:16. He reasoned that nothing in the Phase II study "show[ed] that we have maxed the idea of efficacy" or "reached a ceiling of tolerability." *Id*. 431:2-432:4, 442:2-19. That is, the side effects had not yet reached the level of "dangerous or prohibited," so 720 mg/day is not yet at the "breaking point" for tolerability to be unsafe. *Id*. 429:24-431:1. But a POSA would not have a limited focus to maximizing efficacy up to the tolerability ceiling. Facing chronic treatment of their disease, MS patients were willing to take less efficacious treatments if they were safer and more tolerable. Stobbe Tr. 228:8-22. In February 2007, the only FDA-approved MS disease modifying therapies were the "first line" injectable therapies—the interferons (Rebif, Avonex, or Betaferon) or glatiramer acetate (Copaxone)—and the second line "high efficacy" but "high risk" infusions—natalizumab (Tysabri) or mitoxantrone. *Id.* 389:2-14; DTX495_0003, 0008, 0030; *see* Wynn Tr.

600:7-15; Lindsey Tr. 121:16-122:5. While Dr. Duddy describes these first line therapies as having "low," "moderate[]," or "unimpressive" efficacy, the "bulk of people" in 2007 chose these injectables over the more effective infusions. Duddy Tr. 389:2-10, 487:8-25. A POSA would have developed DMF as the first "oral medication" to target this larger market for a "front-line" MS therapy, which places increased weight on safety, tolerability, and adherence. Stobbe Tr. 228:8-22. Even Biogen recognized the benefit of DMF as "an oral treatment that was safe and effective with similar efficacy to other first line therapies." Dawson Tr. 318:8-319:1.

2. The Lowest Effective DMF Dose Was Expected Between 360-720 mg/day

66. By January 2006, the Phase II results taught a POSA that at least one of the three DMF doses (120, 360, 720 mg/day) was effective to treat MS. Stobbe Tr. 215:11-216:3; DTX320_0003; DTX319_0001. Based on these findings, a POSA reasonably expected the lowest effective dose to be in the range of 120-720 mg/day. Stobbe Tr. 216:4-13, 219:4-16, 241:23-242:8; *see* DDX-313. Within this range, a POSA would have been motivated to administer 480 mg/day DMF, which allowed more preferred twice daily dosing (i.e., 240 mg bid), and dosing according to the known 120 mg increments. Stobbe Tr. 219:4-24; *see* DDX-316.

67. The additional information published in May 2006 provided a POSA further dose-response information. Stobbe Tr. 227:12-228:7; DTX327; DTX329; DTX441. While 720 mg/day significantly reduced MRI brain lesions, 120 and 360 mg/day suggested a trend in efficacy. *Id.* This would have directed a POSA to focus on the range of 360-720 mg/day DMF in search of the lowest effective dose. Stobbe Tr. 223:9-13, 227:12-25; DTX329_0012; DDX-323. In view of these results, a POSA would have been motivated to administer the intermediate DMF dose of 480 mg/day DMF. Stobbe Tr. 229:20-230:13; DDX-326. The 480 mg/day dose is also one of a limited number of doses between 360-720 mg/day, in view of the established dosing increment of 120 mg in the Phase II study and the other prior art teaching how to make and administer DMF oral

capsules in this increment. *Id.*; DTX341_0006; DTX324_0038. Selecting 480 mg/day DMF would have been a "very logical choice" for the additional reason that it offers the benefit of twice daily dosing of 240 mg (the maximum DMF administered at one time in the Phase II study), with a reasonable expectation that it would have been effective. Stobbe Tr. 229:20-230:13.

68. In an apparent effort to salvage Biogen's defense of the written description, Drs. Wynn and Duddy admit the Phase II study indicates that 480 mg/day DMF may be effective. After being impeached, Dr. Wynn said a POSA "wouldn't know" whether 480 mg/day "was likely to be ineffective." Wynn Tr. 689:20-24. He concluded that, based on the Phase II study, "what was unanticipated was the magnitude of the treatment effect, not that it had any treatment effect." *Id*. 719:4-17. Similarly, Dr. Duddy equivocated on his original position during cross-examination, when he conceded that the Phase II study "does not preclude efficacy at 480 [mg/day], it allows for there to be some form of efficacy." Duddy Tr. 488:12-23; *see id.* 489:22-491:4.

D. Any Differences From The Prior Art Would Have Been Obvious To A POSA

69. The asserted claims of the '514 patent collectively recite the following elements: (i) a method of treating MS with a pharmaceutical composition (e.g., tablet or capsule) containing DMF, (ii) at a therapeutically effective amount of 480 mg/day DMF, (iii) administered daily in 2 equal doses, and (iv) for at least 12 weeks. Stobbe Tr. 235:16-236:3; DTX1_0028-29. The Phase II study teaches all of these elements, except for 480 mg/day DMF administered in 2 equal doses. Stobbe Tr. 236:4-237:2. But this claimed method of treating MS would have been obvious to a POSA in view of the Phase II study, and even more so in view of Nilsson and/or the Joshi references. Stobbe Tr. 234:16-235:7. A POSA would have been motivated to combine these prior art references because each is directed to the use of DMF to treat MS. Stobbe Tr. 235:8-15. The motivation to combine these elements with a reasonable expectation of success renders all of the asserted claims *prima facie* obvious, as the PTO has found. *See* DTX345_0025-26;

DTX346_0006, 0034; Stobbe Tr. 237:14-238:13.

70. The prior art teaches all elements of asserted claims 1, 2, 6, 11, 12, and 15 directed to: (i) a method of treating MS with a pharmaceutical composition containing DMF and excipients, (ii) wherein the therapeutically effective amount of DMF is 480 mg/day:

Asserted Claim Elements	Prior Art
Claim 1A: A method of treating a subject in need of treatment for [MS] comprising orally administering to the subject in need thereof a pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of [DMF], [MMF], or a combination thereof, and (b) one or more pharmaceutically acceptable excipients,	The Phase II study teaches a method of treating MS by orally administering a pharmaceutical composition (a capsule) consisting of a therapeutically effective amount of DMF with one or more pharmaceutically acceptable excipients. FOF 53-56. The Joshi references also provide a "clear steer" to focus on treatment of MS with pharmaceutical compositions (tablets or capsules) of DMF. *Id.* 51. Nilsson teaches preparations of DMF pharmaceutical compositions (tablets or capsules) suitable to treat MS. *Id.* 61.
Claim 2: The method of claim 1, wherein the pharmaceutical composition is administered in the form of a tablet, a suspension, or a capsule.	
Claim 6: The method of claim 1, wherein the pharmaceutical composition consists essentially of [DMF] and one or more pharmaceutically acceptable excipients.	
Claim 15A: A method of treating a subject in need of treatment for [MS] comprising orally administering to the subject pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of [DMF] and (b) one or more pharmaceutically acceptable excipients	
Asserted Claim Elements	**Prior Art**
Claim 1B: wherein the therapeutically effective amount of [DMF], [MMF], or a combination thereof is about 480 mg per day.	A POSA would have motivated to determine the lowest effective DMF dose to treat MS, including to provide a more favorable safety and tolerability profile for an oral treatment targeting a front-line MS therapy and to promote patient adherence with a more convenient twice-daily dosing. FOF 62-65. Based on the Phase II study, a POSA would have reasonably expected that the lowest effective dose of DMF is between 360-720 mg/day, including that 480 mg/day DMF is effective to treat MS. *Id.* 66-68.
Claim 11: A method of treating a subject in need of treatment for [MS] consisting essentially of orally administering to the subject about 480 mg per day of [DMF], [MMF], or a combination thereof.	
Claim 12: The method of claim 11, wherein about 480 mg of [DMF] per day is administered to the subject.	
Claim 15B: wherein the therapeutically effective amount of [DMF] is about 480 mg per day.	

71. The prior art teaches all elements of asserted claims 3, 4, 9, 13, and 16 directed to

administering DMF in separate administrations of 2 equal doses:

Asserted Claim Elements	Prior Art
Claim 3: The method of claim 1, wherein the therapeutically effective amount is administered in separate administrations of 2, 3, 4, or 6 equal doses.	In the Phase II study, 120 mg DMF was administered once or thrice daily (120 and 360 mg/day), and 240 mg DMF was administered thrice daily (720 mg/day). FOF 53; *see also id.* 66-67. A POSA also would have known that twice-daily dosing improves patient adherence relative to thrice-daily dosing. *Id.* 63. A POSA would have been motivated to administer 480 mg/day DMF in two equal doses, because it provides improved tolerability and the benefit of twice daily dosing of 240 mg (the maximum DMF administered at one time in the Phase II study), with a reasonable expectation that it would have been effective. *Id.* 66-68.
Claim 4: The method of claim 3, wherein the therapeutically effective amount is administered in separate administrations of 2 equal doses.	
Claim 9: The method of claim 6, wherein the therapeutically effective amount is administered to the subject in 2 equal doses.	
Claim 13: The method of claim 12, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.	
Claim 16: The method of claim 15, wherein the dimethyl fumarate is administered in separate administrations of 2 equal doses.	

72. The prior art teaches all elements of asserted claims 8 and 10 directed to administering the therapeutically effective amount of DMF for at least 12 weeks:

Asserted Claim Elements	Prior Art
Claim 8: The method of claim 1, wherein the pharmaceutical composition is administered to the subject for at least 12 weeks.	The Phase II study administered DMF to patients for 48 weeks. FOF 53. As MS is a chronic disease, it would have been obvious to administer a therapeutically effective amount of DMF to treat MS for at least 12 weeks. Lindsey Tr. 130:5-19; Wynn Tr. 611:24-612:7.
Claim 10: The method of claim 9, wherein the therapeutically effective amount is administered to the subject for at least 12 weeks.	

VII. Alternatively, The Asserted Claims Of The '514 Patent Are Invalid As Anticipated

73. To the extent the '514 patent has adequate written description, Nilsson's equivalent disclosure would anticipate the asserted claims. Stobbe Tr. 245:1-21. As recited in asserted claims 1-4, 6, 9, 11-13, and 15-16, FOF 70-71, Nilsson teaches pharmaceutical compositions suitable to treat a variety of diseases, including MS. Stobbe Tr. 233:23-234:4; DTX324_0039-40 (37:17-38:9), 0041 (39:11-20), 0062 (claims 44-45). These compositions comprise fumaric acid esters,

preferably "DMF" as the active substance, with excipients. Stobbe Tr. 233:7-14; DTX324_0003 (1:4-5), 0009-10 (7:30-37, 8:13-16), 0060 (claim 27). The active substance is administered at a daily dose of 240-1080, including "360 to 480 mg" or "480 to 600 mg" DMF in 1, 2, or 3 doses of an oral capsule or tablet. Stobbe Tr. 233:15-22; DTX324_0037-38 (35:26-36:5), 0038-39 (36:13-37:2). As recited in asserted claims 8 and 10, FOF 72, these compositions may be administered for more than 12 weeks, including "16 weeks." Stobbe Tr. 234:5-10; DTX324_0009 (7:20-21).

VIII. Defendants' Experts

74. Dr. Voon Wee Yong is a neuroscientist at the University of Calgary, where he is a Professor and Head of the Division of Translation of Neuroscience. Yong Tr. 68:4-7, 68:22-69:7; DTX467_0002. He received his Ph.D. from the University of British Columbia in 1986 and his research focuses on "the causes and the pathology of [MS]." *Id*. 68:8-16, 69:8-69:7.

75. Dr. John Lindsey is a Professor of Neurology and a physician at the University of Texas-Houston Medical School. Lindsey Tr. 114:17-115:8; DTX466_0002. He received his M.D. at Harvard Medical School in 1987 and completed his post-graduate training in Neurology at Stanford University Medical Center in 1993. *Id.* He has treated patients with MS for his entire career. Lindsey Tr. 115:9-19. He has served as a principal investigator on several MS clinical studies and has authored or co-authored over 50 peer-reviewed articles. *Id*. 115:9-116:1.

76. Dr. Gary Stobbe is Clinical Associate Professor and neurologist at the University of Washington Medical Center. Stobbe Tr. 201:11-16; DTX464_0002-3. He received his M.D. at the Albany Medical College in 1989 and completed his post-graduate training in neurology at UCLA in 1993. Stobbe Tr. 201:21-202:6. Up until August 2018, about 50% of his neurology practice had a specific focus on the treatment of MS. *Id*. 202:7-17. He opened the MS Center at the University of Washington, where he was an attending neurologist from 2012-2018, and has been involved in several clinical trials for the treatment of MS. *Id*. 202:18-23, 203:21-204:16.

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